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Use of noninvasive and invasive mechanical ventilation in cardiogenic shock: A prospective multicenter study

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ABSTRACT

Background: Despite scarce data, invasive mechanical ventilation (MV) is widely recommended over noninvasive ventilation (NIV) for ventilatory support in cardiogenic shock (CS). We assessed the real-life use of different ventilation strategies in CS and their influence on outcome focusing on the use of NIV and MV.
Methods: 219 CS patients were categorized by the maximum intensity of ventilatory support they needed during the first 24 h into MV ($n = 137$; 63%), NIV ($n = 26$; 12%), and supplementary oxygen ($n = 56$; 26%) groups. We compared the clinical characteristics and 90-day outcome between the MV and the NIV groups.
Results: Mean age was 67 years, 74% were men. The MV and NIV groups did not differ in age, medical history, etiology of CS, PaO_2/FiO_2 ratio, baseline hemodynamics or LVEF. MV patients predominantly presented with hypoperfusion, with more severe metabolic acidosis, higher lactate levels and greater need for vasoactive drugs, whereas NIV patients tended to be more often congestive. 90-day outcome was significantly worse in the MV group (50% vs. 27%), but after propensity score adjustment, mortality was equal in both groups. Confusion, prior CABG, ACS etiology, higher lactate level, and lower baseline PaO_2 were independent predictors of mortality, whereas ventilation strategy did not have any influence on outcome.
Conclusions: Although MV is generally recommended mode of ventilatory support in CS, a fair number of patients were successfully treated with NIV. Moreover, ventilation strategy was not associated with outcome. Thus, NIV seems a safe option for properly chosen CS patients.

1. Introduction

Cardiogenic shock (CS) is defined as a state of critical end-organ hypoperfusion due to reduced cardiac output often resulting in multiorgan failure. The most frequent cause of CS is acute myocardial infarction (AMI), but also other cardiac emergencies can lead to shock [1,2]. Despite remarkable advancement in pharmacological and interventional treatment of AMI over the last decades, mortality in CS remains unacceptably high at 40% to 50% [3,4]. Even though patients presenting with CS are critically ill, their clinical picture can range from mild hypoperfusion to profound treatment-refractory shock. CS patients frequently have significantly elevated pulmonary capillary wedge pressure and

Abbreviations: CS, cardiogenic shock; AMI, acute myocardial infarction; MV, invasive mechanical ventilation; NIV, noninvasive ventilation; APE, acute cardiogenic pulmonary edema; STEMI, ST-elevation myocardial infarction; ACS, acute coronary syndrome; ARDS, acute respiratory distress syndrome; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; CABG, coronary artery bypass grafting; SD, standard deviation; IQR, interquartile range; OR, odds ratio; CI, confidence interval; PCI, percutaneous coronary intervention; ARF, acute respiratory failure.

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consequently are prone to pulmonary oedema and respiratory distress. Most CS patients need some ventilatory support to provide adequate gas exchange and to relieve the work of breathing. Depending of the severity of ventilatory disturbance, some patients may be managed only with supplementary oxygen, whereas those suffering from profound circulatory shock are intubated as a rule.

The majority of guidelines and reviews recommend mechanical ventilation (MV) in CS [5,6]. However, this recommendation is essentially based on expert opinion rather than on scientific data. The role of noninvasive ventilation (NIV) is well established and studied in acute cardiogenic pulmonary edema (APE). It has been shown to reduce respiratory distress and the rate of endotracheal intubation [7–9], but despite several studies and meta-analyses, its impact on mortality is still a matter of debate [10–12]. On one hand, patients presenting with symptoms of shock or ST segment elevation myocardial infarction (STEMI) and those who need urgent coronary revascularization have been excluded from most of these studies [7,8,11,13]. On the other hand, NIV has been formally contraindicated in patients with CS because it may worsen hypotension, and the frequently altered mental status does not ensure adequate spontaneous ventilation. Little is known about the use of different ventilatory support strategies in the treatment of CS. To the best of our knowledge, there are no data comparing the use of NIV and MV in CS. The aim of our study was to analyze the use of different ventilatory support strategies and their impact on 90-day outcome in a large cohort of CS patients.

2. Patients and methods

The CardShock study (ClinicalTrials.gov identifier NCT01374867, registered on 9 June 2011) was conducted at nine European tertiary care hospitals in eight countries between October 2010 and December 2012. The study population, which comprised 219 prospectively enrolled patients with CS, has been described previously [1].

2.1. Inclusion criteria and data collection

Adult patients were enrolled within 6 h from the detection of CS. In addition to an acute cardiac cause, the inclusion criteria were: systolic blood pressure had to be <90 mm Hg (after adequate fluid challenge) for 30 min OR need for vasopressor therapy to maintain SBP > 90 mm Hg AND signs of hypoperfusion (confusion, cold periphery, oliguria <0.5 mL/kg/h for the previous 6 h, or blood lactate >2 mmol/L). Exclusion criteria were shock caused by ongoing hemodynamically significant arrhythmias or shock after cardiac or non-cardiac surgery. The etiology of shock was classified as acute coronary syndrome (ACS) or non-ACS, and the diagnosis was set by the local investigators. Baseline characteristics, medical history, clinical findings and hemodynamic parameters were recorded at detection of shock. Biochemical and hemodynamic data as well as treatment and procedures were registered at baseline and at predefined time points until 96 h after inclusion. Patients were treated according to local clinical practice. Written informed consent was obtained from each patient or a close person or a relative if the patient was unable to give the consent on admission.

Assessing the need for ventilatory assistance and the choice of ventilatory mode (room air, supplementary oxygen, NIV or MV) were at the discretion of the physician in charge and based on common indications and contraindications for NIV and MV treatment. Arterial blood gas samples were analyzed locally at baseline and at pre-specified time points thereafter. PaO_2/FiO_2 ratio was calculated using the measured PaO_2 and reported FiO_2. The degree of hypoxemia and respiratory failure was classified according to Berlin definition ARDS (acute respiratory distress syndrome) criteria: mild (200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg), moderate (100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg), and severe (PaO_2/FiO_2 ≤ 100 mm Hg) [14]. Estimated glomerular filtration rate (eGFR) was calculated from creatinine values using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [15].

We categorized the patients by the maximum intensity of ventilatory support during the first 24 h in three groups: invasive MV group, NIV group (including both continuous positive airway pressure and bilevel positive airway pressure) and supplementary oxygen group (including patients treated with supplementary oxygen only by mask or nasal cannulas). We analyzed their clinical characteristics, treatment and outcome. The supplementary oxygen therapy group was not included in further comparisons. Patients who died during the first 24 h were included if they received NIV or MV treatment. The primary endpoint was all-cause 90-day mortality; three patients were lost to follow up. NIV failure was defined as requirement for endotracheal intubation after NIV as a first line ventilatory support mode. Vital status during follow-up was determined through direct contact with the patient or next of kin, or through population and hospital registers. The study was approved by local ethics committees (detailed later after discussion) and conducted in accordance with the Declaration of Helsinki.

2.2. CardShock risk Score

The CardShock risk Score is a risk prediction model for in-hospital mortality in CS that has been created by using the variables which independently associated with all-cause death in the CardShock study [1]. The Score consists of seven parameters [age >75 years, eGFR, blood lactate, confusion on admission, left ventricular ejection fraction (LVEF) <40%, previous myocardial infarction (MI) or coronary artery bypass grafting (CABG), and ACS etiology] giving a maximum of nine points. Patients can be classified according to the risk Score into low, intermediate, and high risk groups regarding in-hospital mortality.

2.3. Statistical analysis

Results are presented as numbers (n) and percentages (%) for categorical variables, and for continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Chi-squared test and Fisher's exact test were used to compare categorical variables, and Student's *t*-test, Wilcoxon signed rank test and Mann–Whitney *U* test were used for continuous variables, as appropriate. Multivariable logistic regression analysis was used to determine independent risk factors for 90-day mortality. In order to avoid model over-fitting, independent predictors of 90-day mortality were identified from selected variables known to be clinically related to outcome. The model was also adjusted for CardShock Risk Score variables, age, gender, and participating center. Results from the regression analyses are presented as odd ratios (OR) with 95% confidence intervals (CI).

Propensity score adjustment was used to diminish bias and increase precision in analyses assessing the relationship between ventilatory treatment and mortality [16]. Propensity score was created using logistic regression modeling the likelihood of a patient receiving either NIV or MV. Variables were chosen based on clinical relevance and on potential or observed association with outcome [1]. The final propensity score was estimated with the following variables: age, gender, medical history (myocardial infarction, coronary artery bypass graft surgery, diabetes mellitus, hypertension), acute coronary syndrome etiology, and initial presentation (confusion, blood lactate, systolic blood pressure, non-sinus rhythm, left ventricular ejection fraction, and estimated glomerular filtration rate (CKD-EPI)). The score estimate was transformed into logit scale [17]. The Kaplan-Meier method was used for unadjusted and the Cox regression for adjusted survival analyses; the assumption of proportional hazards was checked with parallelism of log-log survival curves. The variables included in the propensity score adjustment analysis are stated below the Fig. 1. A two-sided *p*-value <0.05 was regarded as statistically significant. All statistical analyses were performed with SPSS 22.0 statistical software (IBM Corp, Armonk, NY, USA).

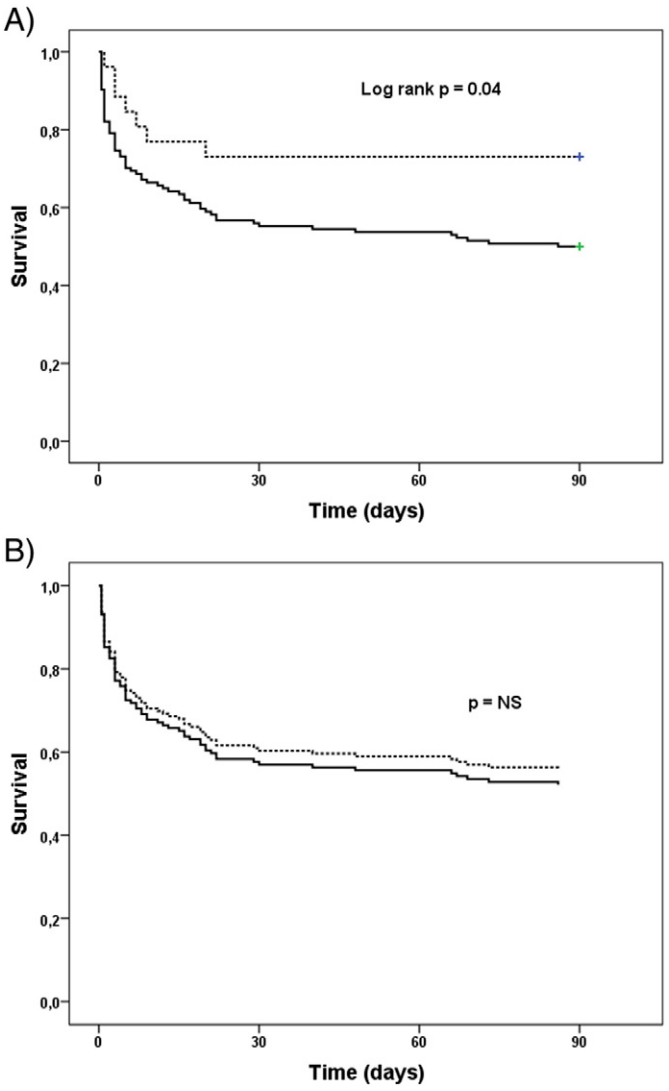

Fig. 1. A) Unadjusted (Kaplan Meier) and B) propensity score adjusted (Cox regression) survival curves for the use of MV (solid line) and NIV (dashed line). MV, invasive mechanical ventilation group; NIV, noninvasive ventilation group. Adjusted for logit of the propensity score, which was estimated with the following variables: age, gender, medical history (myocardial infarction, coronary artery bypass graft surgery, diabetes mellitus, hypertension), acute coronary syndrome, and initial presentation (confusion, blood lactate, systolic blood pressure, non-sinus rhythm, left ventricular ejection fraction, and estimated glomerular filtration rate (CKD-EPI)).

3. Results

3.1. Study population

A total of 219 patients were included in the study. The main characteristics of the study population are summarized in Table 1. Briefly, the mean age was 67 (SD 12) years, and 26% were women. ACS was the most frequent cause of CS (81%, $n = 177$). At baseline, the blood pressure was on average 78/40 mm Hg and heart rate 90 beats per minute. Median length of hospital stay was 12 (IQR 7–25) days, and 90-day mortality was 41%.

3.2. Mechanical ventilation (MV) and noninvasive ventilation (NIV)

During the first 24 h, 30 patients were initially treated with NIV. Eight of these patients had to be intubated (NIV failure). Half of the failures occurred during the first 24 h, and the rest later during the subsequent 24 to 96 h. Those four patients initially treated with NIV and shifted to MV during the first 24 h have been included in the MV group. In comparing ventilation modes, 63% ($n = 137$) of the patients were classified as treated with MV, and 12% ($n = 26$) with NIV. Clinical characteristics and baseline information of the patients who required oxygen only by mask or nasal cannula ($n = 56$; 26%) are presented in Tables 1-3 as a "Supplementary oxygen group". Because this group differs from the NIV and the MV groups, especially with regard to the severity of the respiratory failure (Table 3), it was not included in further comparisons.

Clinical characteristics between the MV and the NIV groups are compared in Table 1. There were no significant differences between the groups in age, gender, or medical history. In both groups, over 50% of the patients were smokers or ex-smokers, but few had a diagnosed chronic lung disease. The proportion of patients with ACS etiology of CS was similar in both groups. Clinical presentation and biochemistry at baseline are shown in Tables 1 and 2. The NIV group had slightly higher systolic blood pressure, but the groups did not differ otherwise in hemodynamic parameters or LVEF at baseline. Patients in the MV group were more often confused (83% vs. 31%, $p < 0.001$) and had higher lactate levels (3.7 vs. 1.7 mmol/L, $p < 0.001$). MV patients also received vasoactive medication more frequently (norepinephrine 88% vs. 69%, $p = 0.03$; dobutamine 61% vs. 27%, $p = 0.001$), with the exception of levosimendan (22% vs. 58%, $p < 0.001$) that was administered more often to patients in the NIV group. Noninvasively ventilated patients had higher hs-TnT (3631 vs. 1597 ng/L; $p = 0.06$) and NT-proBNP (7375 vs. 2367 ng/L; $p = 0.04$) levels (Table 2). Revascularization rates did not differ between the groups. Forty percent of MV patients had been resuscitated before inclusion into the study.

3.3. Ventilatory parameters and mortality

Ventilatory parameters at baseline and at 24 h are presented in Table 3. Patients treated with MV suffered from metabolic acidosis more often and were treated with higher oxygen fraction at baseline compared with NIV group. The MV group had also slightly higher PaO_2 and $PaCO_2$ levels. In terms of PaO_2/FiO_2 ratio, the degree of respiratory failure was moderate in both groups at baseline but improved with both respiratory modalities during the first 24 h. The level of positive end-expiratory pressure (PEEP) ranged in the NIV group from 5 to 12 cmH_2O with a median level of 8 cmH_2O (IQR 7.5–10) and in the MV group from 4 to 14 cmH_2O with a median level of 6 cmH_2O (IQR 5–8), respectively. The duration of the ventilation was significantly longer in the MV group.

Outcome and length of stay for each group are shown in Table 2. In-hospital mortality was 45% in the MV group and 19% in the NIV group ($p = 0.01$), and 90-day mortality was 49% and 27% ($p = 0.03$), respectively. However, after adjustment for severity of disease using variables of the CardShock risk Score, ventilation strategy had no influence on the 90-day outcome. The results remained unchanged when ventilation strategy was analyzed up to 96 h. Interestingly, higher PaO_2 at baseline was independently associated with better outcome. Whether the patient was resuscitated or not did not have an effect on outcome when tested in multivariable analysis. Adjusted ORs for variables associated with 90-day mortality are shown in Table 4. The propensity score adjustment analysis confirmed that ventilation strategy did not influence the mortality rate (Fig. 1). We performed an additional propensity score analysis excluding the resuscitated patients but this did not affect the results (Supplementary material online, Fig. S1).

4. Discussion

To our knowledge, this prospective multinational study is the first to provide information about contemporary use of different ventilation modalities in CS. First, we found that while the majority of patients were intubated and mechanically ventilated, one fourth did not need ventilatory support at all. Second, NIV treatment was used successfully

Table 1
Patient characteristics and etiology of cardiogenic shock.

	All ($n = 219$)	MV ($n = 137$)	NIV ($n = 26$)	p-Value*	Supplementary oxygen ($n = 56$)
Age, years	67 (12)	66 (11)	66 (12)	0.8	68 (13)
Women, n (%)	57 (26)	31 (23)	8 (31)	0.4	18 (32)
BMI	26.9 (4.2)	27.4 (3.9)	26.4 (4.3)	0.3	25.8 (4.5)
Medical history, n (%)					
Coronary artery disease	76 (35)	51 (37)	10 (39)	0.9	15 (27)
Previous MI	54 (25)	35 (26)	8 (31)	0.6	11 (20)
Prior CABG	16 (7)	11 (8)	4 (15)	0.3	1 (2)
Heart failure	36 (16)	25 (18)	3 (12)	0.6	8 (14)
Hypertension	132 (60)	85 (62)	17 (65)	0.7	30 (54)
Diabetes	62 (28)	44 (32)	6 (23)	0.4	11 (20)
Asthma or COPD	25 (11)	18 (13)	2 (8)	0.7	5 (9)
Smoker or ex-smoker	135 (62)	95 (69)	14 (54)	0.2	26 (47)
Etiology of cardiogenic shock, n (%)					
ACS	177 (81)	111 (81)	20 (77)	0.6	46 (82)
non-ACS	42 (19)	26 (19)	6 (23)	0.6	10 (18)
STEMI	148 (68)	87 (64)	18 (69)	0.6	43 (77)
Resuscitated, n (%)	62 (28)	55 (40)	0		7 (13)

Data are presented as numbers and percentages (%), mean (SD), and median (IQR).
* p-Values are for the difference between MV and NIV group. MV, invasive mechanical ventilation group; NIV noninvasive ventilation group; BMI, body mass index; SD, standard deviation; MI, myocardial infarction; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction.

in 12% of patients. Third, most important find, was that NIV was not associated with increased mortality even after adjustment for severity of disease. Fourth, higher PaO_2 on admission was associated with better prognosis.

There are scarce data available on the use of different respiratory modalities in CS. In the AHEAD (Acute Heart Failure Database) registry study, 8% of the subgroup of CS ($n = 600$) were treated with NIV and 56% with MV [18]. Only 11.6% of these CS patients underwent coronary angiography, suggesting a different patient population compared to the patients in our study, in whom coronary angiography was performed in 83%. In another British study assessing the outcome of CS patients undergoing percutaneous coronary intervention (PCI), only 28.4% were treated with MV [19]. This contrasts with the IABP-SHOCK II trial, in which 80% of patients were mechanically ventilated [20]. A recent French registry study reported that in intensive care units 75% of CS patients were treated with MV and 7% with NIV [21]. Contrary to this study we recruited patients from emergency departments, cardiac and intensive care units, as well as catheter laboratories, and thus included probably also milder forms of shock which can account for the smaller need for MV in our study. In addition, the shock was caused by AMI in only 12% of the patients differing clearly from our population. Our multinational, multicenter study shows that the majority of CS patients indeed are treated with ventilatory support, mostly with MV, but also with NIV with success.

The overall mortality of 41% observed in our study is comparable with other recent studies on CS [4,19,22,23]. The 90-day mortality was

Table 2
Physiologic parameters at baseline, mortality, and length of ICU/CCU and hospital stay.

	All ($n = 219$)	MV ($n = 137$)	NIV ($n = 26$)	p-Value*	Supplementary oxygen ($n = 56$)
Clinical findings					
Systolic blood pressure, mmHg	78 (14)	78 (15)	83 (10)	0.03	75 (11)
Heart rate, beats per minute	90 (28)	91 (29)	87 (23)	0.2	89 (29)
LVEF, %	33 (14)	32 (14)	33 (12)	0.7	36 (17)
Confusion, n (%)	148 (68)	113 (83)	8 (31)	<0.001	26 (46)
Biochemistry					
Blood hemoglobin, g/L	128 (22)	130 (23)	125 (22)	0.3	124 (24)
Arterial blood lactate, mmol/L	2.8 (1.7–5.8)	3.7 (2.2–7.0)	1.7 (1.4–2.8)	<0.001	2.3 (1.6–3.5)
hsTnT, ng/L	2190 (388–5418)	1597 (337–4178)	3631 (1289–10,170)	0.06	2427 (418–7459)
NT-proBNP, pg/mL	2710 (585–9434)	2367 (559–8563)	7375 (2053–17,372)	0.04	1860 (511–8976)
Creatinine, mmol/L	104 (78–140)	110 (87–144)	100 (69–119)	0.1	107 (84–140)
eGFR, mL/min/1.73 m^2	61 (41–87)	64 (30)	67 (28)	0.6	59 (28)
CRP, g/L	16 (4–54)	15 (4–49)	37 (6–79)	0.2	15 (4–48)
Management, n (%)					
Coronary angiography	182 (83)	114 (83)	23 (89)	0.8	45 (80)
PCI	149 (68)	90 (66)	19 (73)	0.5	40 (71)
CABG	9 (4)	5 (4)	3 (12)	0.1	1 (2)
IABP	122 (56)	85 (62)	16 (62)	1.0	21 (38)
Mortality, n (%)					
In-hospital mortality	80 (37)	62 (45)	5 (19)	0.01	13 (23)
90-day mortality	89 (41)	67 (49)	7 (27)	0.03	15 (27)
ICU/CCU length of stay, days	5 (2 − 10)	6 (2 − 11)	4 (2–8)	0.2	3 (1–7)
In-hospital length of stay, days	12 (7–25)	17 (10–27)	12 (7–27)	0.2	8 (4–18)

Data are presented as numbers and percentages (%), mean (SD), and median (IQR).
* p-Values are for the difference between MV and NIV groups. MV, invasive mechanical ventilation group; NIV noninvasive ventilation group; LVEF; left ventricular ejection fraction; hsTnT, highly sensitive troponin; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump; ICU, intensive care unit; CCU, cardiac care unit.

Table 3
Arterial blood gas values, ventilatory parameters at baseline and at 24 h, and duration of ventilation.

	MV (n = 137)	NIV (n = 26)	p-Value*	Supplementary oxygen (n = 56)
At baseline				
pH	7.27 (7.17–7.34)	7.39 (7.32–7.43)	<0.001	7.38 (7.30–7.44)
PaO_2, kPa	12.9 (10.4–18.6)	11.2 (9.9–15.0)	0.2	13.40 (9.2–16.8)
$PaCO_2$, kPa	5.5 (4.9–6.4)	4.5 (4.2–5.9)	0.01	4.9 (3.9–5.6)
HCO_3, mmol/L	19.6 (15.9–21.5)	22.0 (20.5–24)	0.001	21.9 (16.7–23.4)
FiO_2, %	76 (22)	60 (19)	0.001	32 (26)
P/F ratio, mm Hg	141 (97–211)	167 (107–215)	0.3	311 (200–358)
200–300 mm Hg, n (%)	35 (26)	7 (27)	0.9	7 (13)
100–200 mm Hg, n (%)	54 (40)	14 (54)	0.2	7 (13)
<100 mm Hg, n (%)	40 (29)	4 (15)	0.1	0
At 24 h				
pH	7.40 (7.35–7.43)	7.42 (7.38–7.46)	0.05	7.43 (7.40–7.46)
PaO_2, kPa	12.1 (10.5–14.0)	11.8 (10.4–13.6)	0.5	11.1 (10.0–13.1)
$PaCO_2$, kPa	5.30 (4.70–5.70)	4.50 (4.20–4.90)	< 0.001	4.8 (4.3–5.5)
HCO_3, mmol/L	24 (21.3–26.3)	23 (21–25)	0.2	24 (21–25)
FiO2, %	52 (18)	53 (23)	0.8	27 (17)
P/F ratio, mm Hg	192 (138–265) [1,2]	191 (136–284) [2]	1.0	302 (239–396)
200–300 mm Hg, n (%)	33 (24)	6 (23)	0.9	7 (13)
100–200 mm Hg, n (%)	46 (34)	8 (31)	0.7	3 (5)
<100 mm Hg, n (%)	13 (10)	3 (12)	0.7	0
Duration of ventilation, h	94 (30–184)	41 (28–71)	0.007	

Data are presented as numbers and percentages (%), mean (SD), and median (IQR).
MV, invasive mechanical ventilation group; NIV noninvasive ventilation group; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood, FiO_2, fraction of inspired oxygen; P/F ratio, PaO_2/FiO_2 ratio.
* p-Values are for the difference between MV and NIV groups. 1) the improvement during the 24 h was significant in the MV group, 2) but not between the groups.

higher in the MV group. After accounting for the possible imbalance of multiple covariates and baseline characteristics by using propensity score method, the ventilation strategy did not have an effect on outcome. The outcome of patients treated with NIV was better in our study than in the AHEAD study, which showed a 62.7% in-hospital mortality in the NIV group, and an even worse prognosis for those treated with MV, whose in-hospital mortality was 71.8% [18].

Compared to patients treated with NIV, those requiring MV were more often confused, had metabolic acidosis, higher lactate levels, and greater need for vasoactive drugs indicating a more severe tissue hypoperfusion and shock, whereas the NIV group had higher NT-proBNP levels, possibly indicating a greater distension of the ventricles and elevated filling pressure. In terms of PaO_2/FiO_2 ratio, the degree of acute respiratory failure (ARF) at baseline was moderate in both groups and improved equally during the first 24 h with both respiratory modalities. Since the degree of respiratory failure improved equally with both ventilation strategies, probably the more severe shock and hypoperfusion accounted for the longer duration of the ventilation in the MV group.

In general, there are no specific recommendations concerning indications for NIV or intubtion and MV in CS except in isolated right ventricular failure, where caution is advised due to possible undesirable effect of positive end-expiratory pressure on right ventricular afterload and function. Our study suggests that CS patients with congestion and mild-to-moderate respiratory failure, able to co-operate, and without signs of severe hypoperfusion can be safely treated with NIV. Success rate of NIV during the first 24 h was 87%, which is higher than in previous studies assessing the use of NIV in ARF in intensive care units [24–26]. However, patients who do not improve with NIV treatment should be promptly intubated, and NIV trial should not delay intubation and mechanical ventilation when needed. It is also crucial to start the NIV treatment in a very early phase of respiratory failure, preferably already in the out-of hospital setting [27,28].

There are several advantages in NIV compared with MV. NIV allows patients to communicate, eat, move at least to some extent, and breathe spontaneously. By avoiding endotracheal intubation and invasive MV, the risks of nosocomial infections, ventilator-associated pneumonia and injuries related to the intubation procedure itself are diminished [29,30]. By using NIV instead of MV, the administration of complete sedation with loss of vasomotor tone can be avoided. This might be especially beneficial in patients presenting with symptoms of shock, in whom the sedatives may increase hypotension.

Higher PaO_2 at baseline predicted improved outcome independently. This is striking, since studies assessing the impact of hyperoxemia on outcome during critical illness have demonstrated excess oxygen to be harmful [31]. Arterial hyperoxia has been shown to induce vasoconstriction and reduce cardiac output, which may impair blood flow to the organs at risk [32]. Indeed, these effects could be considered especially harmful in CS. However, there are several important differences between these studies assessing the role of hyperoxemia on outcome and the present one. First, the previous studies have focused only on certain patient populations, e.g. patients with cardiac arrest, traumatic brain injury or stroke, and thus probably cannot be generalized into general intensive care unit population. Second, the level of hyperoxemia among the studies has varied and has in some of the trials been 40 kPa (300 mm Hg) or even more [33], which is clearly higher than the average PaO_2 level in our study. Furthermore, some of the studies excluded patients presenting with hypoxemia [(PaO_2/FiO_2 ratio <27 kPa (200 mm Hg) or PaO_2 <8 kPa (60 mm Hg)] [33], whereas most of the patients in our study had PaO_2/FiO_2 ratio below 27 kPa (200 mm Hg). However, there are preliminary data indicating that by inducing peripheral vasoconstriction, hyperoxemia may prevent shock-induced hypotension and decrease the need for use of vasopressor and thus help to stabilize hemodynamics in vasodilatory shock [34]. In the present

Table 4
Multivariable regression analysis for 90-day mortality.*)

Variable	Adjusted OR (95% CI)	p-Value
Age > 75 years	1.62 (0.45–5.86)	0.47
Confusion	5.22 (1.30–21.00)	0.02
Prior CABG	25.57 (1.57–417.76)	0.02
ACS etiology	4.69 (1.13–19.46)	0.03
Ventilation mode**)	0.85 (0.15–4.80)	0.85
eGFR (per 10 mL/min/1.73 m^2 increase)	0.96 (0.78–1.19)	0.72
LVEF (per 10% increase)	0.79 (0.50–1.25)	0.31
Lactate (per mmol/L increase)	1.47 (1.17–1.84)	0.001
PaO_2 (per kPa increase at baseline)	0.93 (0.88–0.99)	0.02

OR, odds ratio; CI, confidence interval; CABG, coronary artery bypass grafting; ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.
* The mode included also variable accounting for participating center and sex.
** The reference factor is NIV.

study, the severity of shock and underlying cardiovascular status were clearly the main determinants of prognosis, whereas the ventilation strategy did not have an effect on outcome.

Guidelines do not recommend using NIV in patients presenting with ACS or APE and suffering from shock or low blood pressure, or requiring urgent coronary revascularization [5,6,35]. In many studies regarding the use of NIV in APE or ARF, the presence of low blood pressure, need for vasoactive medication or shock have been considered as exclusion criteria or as criteria for intubation [7,8,13,36,37]. In our experience, NIV is feasible during angiography and PCI, and the study results suggest that NIV can be safely used in patients presenting with severe hemodynamic impairment treated with vasoactive drugs. Our findings are also supported by a recently published propensity-based analysis, which demonstrated that presence or absence of shock did not have an effect on mortality in APE patients treated with CPAP [38].

4.1. Limitations

There are some limitations to be acknowledged. First, although the CardShock study was prospective and included a reasonable number of patients, the limited number of patients treated with NIV decreased the statistical power in between-group comparisons. Second, the choice of ventilation strategy was at the discretion of the physician in charge. However, the study reflects real life practice in European tertiary care hospitals. Third, the study lacks randomization and confounding by indication is a possible bias. We used regression and propensity score methods to minimize this bias, and though differences in some unmeasured confounding variables cannot be excluded, the results regarding the safety of NIV use were consistent. Finally, the number of patients in the NIV group from whom a complete serial blood gas data was available was limited, and caution in the interpretation of the results is advocated.

5. Conclusions

In this observational multicenter study, we observed that NIV can be safely used in properly selected patients in cardiogenic shock. Ventilation strategy did not affect outcome. In conclusion, it seems that in highly skilled centers, NIV can be used in the treatment of respiratory failure in CS. However, appropriate patient selection and close monitoring during the treatment are crucial, and NIV trial should not delay intubation and mechanical ventilation when indicated.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.12.175.

Ethics committees

Athens: Ethics Committee of Attikon University Hospital; Barcelona: Health Research Ethics Committee of the Hospital de Sant Pau; Brescia: Ethics Committee of the Province of Brescia; Brno: Ethic committee of University hospital Brno; Helsinki: The Ethics Committee, Department of Medicine, The Hospital District of Helsinki and Uusimaa; Porto: Ethics committee of S. João Hospital Center/Porto Medical School; Rome: Ethical Committee Sant'Andrea Hospital; Warsaw: Local Bioethics Committee of the Institute of CardiologyCopenhagen: By Danish law (https://www.retsinformation.dk/forms/r0710.aspx?id=137674) scientific projects only using information from existing registries does not require approval from a scientific ethical committee. Thus, Ethical approval and informed consent was not required from the Danish Ethical Committee since this study was conducted in a public organization using encrypted personal data. The study was approved by the Danish Protection Agency with reference number GEH-2014-013; I-Suite number: 02731.

Competing interests

V.-P.H. has served on advisory boards for Bayer, BMS/Pfizer, Boehringer-Ingelheim, Roche Diagnostics, Novartis, and Servier, and received lecture fees from Bayer, Orion Pharma, Resmed, and Roche Diagnostics. J.L. has received consulting and/or lecture fees from Boeringer-Ingelheim, Roche Diagnostics, Novartis, Orion Pharma, Pfizer, Servier, and Vifor Pharma. A.S. has served on advisory board for Orion Pharma, and received lecture fees from Astra-Zeneca, Bayer, Menarini, Novartis and Servier. V.C. has received an unrestricted research grant from CVie Therapeutics Limited and consulting honoraria from Servier. J.P. received honoraria for lectures from Orion Pharma and Novartis International. J.M. has received speaker fees and travel grants from Novartis, Menarini, Orion, and Thermo Fisher, and consulting honoraria from Cardiorentis. M.H., T.T., J.S., H.T., M.B., and M.G.L. reported having no disclosures.

Authors' contributions

MH analyzed and interpreted the data and drafted the manuscript. TT assisted analyzing the data. V-PH, JL, TT and JM helped interpreting the results and contributed substantially to the development of the manuscript. All the authors revised the manuscript critically and read as well as approved the final manuscript.

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